Introduction and Rapid Spread of SARS-CoV-2 Omicron Variant and Dynamics of BA.1 and BA.1.1 Sublineages, Finland, December 2021

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Multiple introductions of SARS-COV-2 Omicron variant BA.1 and BA.1.1. lineages to Finland were detected in early December 2021. Within 3 weeks, Omicron overtook Delta as the most common variant in the capital region. Sequence analysis demonstrated the emergence and spread through community transmission of a large cluster of BA.1.1 virus.

The most recent SARS-CoV-2 variant of concern, Omicron (Pango lineage B.1.1.529), was first detected in South Africa (*1*), although it might have emerged elsewhere, and has since spread globally at an unforeseen speed. Notable examples include a superspreading event in Norway (*2*) and the rapid increase in incidence in Denmark (*3*) despite high vaccination coverage (83% of infected persons had received 2–3 vaccine doses). This rapid spread indicates the novel variant's exceptional transmissibility, as well as its potential for reinfection and vaccination breakthrough. We describe the genotypes of cases of Omicron entering Finland from their early spread up to established community transmission through the first week of January 2022. No ethics approval was needed because this study was based on routine COVID-19 surveillance data. The study regarding Helsinki University Hospital (HUH) samples was approved by the local ethical and research committee (Helsinki and Uusimaa Hospital District [HUS]; Clinical microbiology of COVID-19: diagnostics, laboratory findings and biorisks; HUS/244/2021).

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The Study

A total of 99,988 samples found positive for SARS-CoV-2 by reverse transcription PCR, 12.1% of 825,006 total samples tested, were detected in Finland during the study period, November 29, 2021–January 6, 2022 (Figure 1). Weekly positivity rates among persons tested rose from 6.1% of 156,077 in week 48 to 25.6% of 172,451 (3.1% of the Finnish population) in week 52 (https://sampo.thl.fi). In HUS, test positivity increased from 5.0% to 36.7% over the corresponding weeks 48–52. After a change in testing strategy favoring home antigen testing, the number of registered SARS-CoV-2 cases dropped (Appendix, https://wwwnc.cdc.gov/EID/article/28/6/22-0515-App1.pdf).

We estimated the proportions of Omicron variant lineages BA.1 and BA.1.1 within HUS by comparing PCR-based data on S-gene target failure (SGTF) to that of other circulating lineages (Figure 1; Appendix). The results showed a decrease in SGTF rates from week 24, when the proportion of the Alpha variant (B.1.1.7) was declining, to near 0 when the Delta variant (B.1.617.2) was dominant. This decrease aligns well with sequence-confirmed lineage turnover

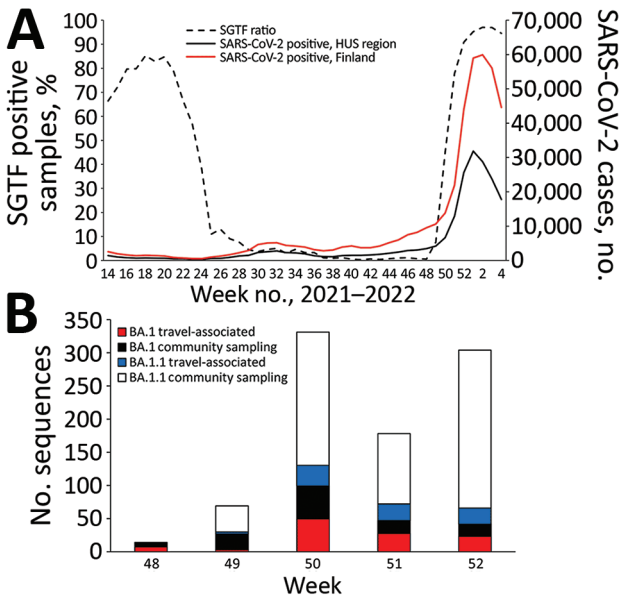

Figure 1. Introduction and spread of SARS-CoV-2 Omicron variant in Finland in late 2021–early 2022. A) Confirmed SARS-CoV-2 positives in Finland (red) and in the HUS region (black) and the proportion of SGTF measured by reverse transcription PCR–positive cases analyzed by the HUS Clinical Microbiology division (dashed line) from week 14 in 2021 through week 4 in 2022 (National Infectious Disease Registry, https://www.thl.fi/ttr/gen/rpt/tilastot.html). B) Weekly numbers of travel-associated and community sampling–derived Omicron cases (Pango lineages BA.1 and BA.1.1) for weeks 48–52, 2021. Travel-associated status was defined by either being sampled at a border or a patient record indicating most likely country of infection abroad. The lower amount of sequences obtained for week 51 originates most likely from the Christmas holiday season. Week 52 was the last full week of our study period. HUS, Helsinki and Uusimaa Hospital District; SGTF, S-gene target failure

reported elsewhere (4). Thereafter, the proportion of SGTF rose steeply from week 48 of 2021 until it reached 97% in week 2 of 2022 (Figure 1), indicating a rapid spread of the BA.1 and BA.1.1 lineages in the capital region of Finland.

The sequenced samples consisted of randomly selected population samples and samples collected at border entry (through airports, harbors, and land borders) to Finland (Table). In addition, a small proportion was preselected based on SGTF positivity (Appendix). Omicron sequence data consisted of 962 sequences, 33.4% of all sequenced samples (n = 3,100; ≈2% of all confirmed cases), during November 29, 2021–January 6, 2022. We collected 133 samples at points of border entry and recorded the number of patients in each hospital district, demographic distribution, and travel status (Table), including countries of origin for the travel-associated cases (Appendix Figure 2). In addition, we added 15 Omicron sequences obtained from hospitalized patients in HUH to the sequence dataset (Appendix Table 1).

We identified Omicron cases in 5 travelers returning to Finland from Sweden through Denmark during November 29–30, 2021. All 5 members of the travel party, who lived in 3 different hospital districts (HUS, Hospital District of Southwest Finland, and North Savo Hospital District), were found to be Omicron positive through PCR testing and sequencing. The identified sequences clustered together with reference sequences mainly from Denmark and Sweden. However, introduction from this travel party did not lead to wide community circulation.

Table. Patient data for 979 sequenced Omicron genomes in investigation of SARS-CoV-2 Omicron variant and dynamics of BA.1 and BA.1.1 sublineages, Finland, December 2021*

Variables	No. (%)†
Sex	
M	513 (52.4)
F	466 (47.6)
Travel	
Abroad	57 (5.8)
Border‡	20 (2.0)
Finland	234 (23.9)
Border‡	6 (0.6)
NA§	688 (70.3)
Border‡	107 (10.9)
Age, y	
Range	0–98
Mean	36.2
Median	34
Sample origin	
HUS	662 (79.7)
Non-HUS total¶	169 (20.3)
Non-HUS by district, no.	
Central Finland Health Care District	6
Central Ostrobothnia Hospital District	6
East Savo Hospital District	3
Hospital District of South Ostrobothnia	10
Hospital District of Southwest Finland	18
Kainuu Social and Health Care Joint Authority	5
Tavastia Proper Hospital District	3
Kymenlaakso Social and Health Services	7
Lapland Hospital District	4
North Karelia Social and Health Care Authority	17
North Ostrobothnia Hospital District	15
North Savo Hospital District	12
Pirkanmaa Hospital District	10
Päijät-Häme Hospital District	3
Satakunta Hospital District	20
South Karelia Social and Health Care District	12
South Savo Social and Health Care Authority	5
Vaasa Hospital District	6
Åland Hospital District	7
Other sample origin	
HUH	15 (1.5)
Border	133 (13.6)

*NA, not available; HUH, Helsinki University Hospital; HUS, Helsinki and Uusimaa Hospital District; Non-HUS, hospital district other than HUS.
†Unless otherwise indicated.
‡Border, samples collected from border entry (airports, harbors, and land).
§Travel data not available, probably originating from Finland.
¶Other, sample collection based on other than hospital districts.

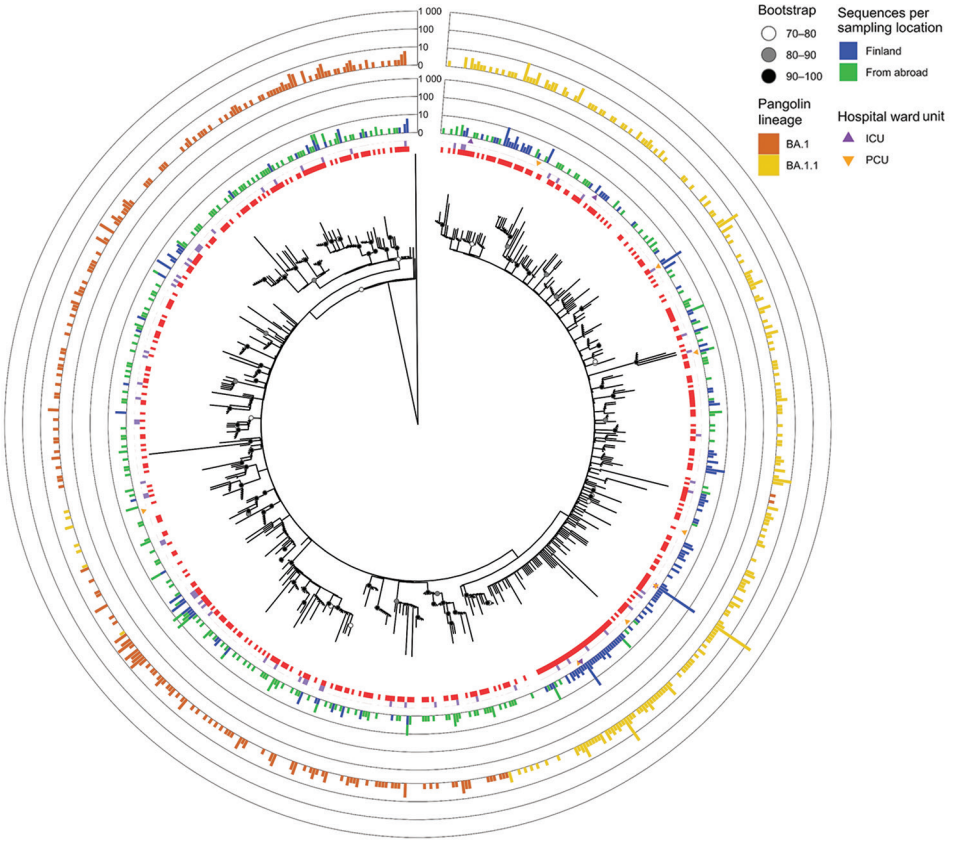

Figure 2. Clustering analysis of Omicron sequences in study of SARS-CoV-2 Omicron variant in Finland in late 2021–early 2022. The collapsed maximum-likelihood phylogenetic tree shows Omicron genomes sampled in Finland (n = 870) and reference sequences from other countries (n = 754), the reference dataset we used. The outermost bar plot shows the number of BA.1 and BA.1.1 sequences in each cluster. Purple squares indicate Omicron sequences collected from a Finland border; clusters with border samples each contain 1–9 sequences. Clustering analysis revealed that, by the beginning of January 2022, aside from 1 major BA.1.1 cluster (n = 236, 27.1% of all cases in Finland during the study period, November 29, 2021–January 6, 2022), most (n = 634, 72.8% of cases) Omicron cases in Finland were either singletons or small clusters (≤30 sequences). The tree was inferred using the IQTREE2 version 2.0.6 (http://www.iqtree.org) using ModelFinder and 1,000 bootstraps were computed with the integrated Ultrafast bootstrap algorithm and the clusters (red squares) with TreeCluster version 1.0.3 (https://github.com/niemasd/TreeCluster) using an arbitrary branch length of 0.001 and support value of 70. Triangles indicate sequences recorded from patients in the ICU or PCU. The tree is rooted to an Omicron BA.2 sequence (Genbank accession no. OV698431.1). ICU, intensive care unit; PCU, pulmonary care unit.

After the first introduction events, the number of weekly sequence-confirmed Omicron cases rose sharply during weeks 49 and 50 (Figure 1, panel B). Although weekly numbers of travel-associated (most likely imported) cases of lineage BA.1 did not differ from those for BA.1.1 ($\chi^2 = 1.03$; p = 0.5975), the proportion of BA.1.1 in the community samples was significantly higher than that of BA.1 (2-sample z-test, p = 0.0024, week 49 vs. week 50; Appendix Figure 3.). We did not detect lineage BA.2. during the study period.

Our phylogenetic and clustering analysis (Figure 2; Appendix Figure 1) inferred 80 small, highly supported lineage BA.1 subclusters that contained sequences (n = 168) from Finland, as well as 47 BA.1 sequences that were singletons or from low-support clusters. For BA.1.1 sequences, the analysis inferred 129 clusters containing BA.1.1 sequences (n = 570) from Finland and 75 singletons. Of note, among BA.1.1 clusters, 1 cluster contained 236 identical sequences, 24.5% of all Omicron sequences from Finland recorded during the study period. These sequences were also identical to isolate HKU-344 (OM212473) from Hong Kong, collected November 27, 2021. These identical sequences were detected starting December 7 through the end of the study period. Most of these cases, 197/236 (83.5%), were detected in HUS, including the first 2 cases on December 7. Eleven of the sequences from this clade were imported, with the most likely countries of infection reported as Estonia (December 9, 2021), Sweden (December 15), and the United Kingdom, Spain, or Portugal (all December 20). An additional 8 cases were sampled at the border during December 15–21; 1 originated from Sweden, but no data were available about the country of infection for the other cases. Although the analysis of imported cases suggested that a virus of identical genotype was circulating in several European countries, locally acquired infections of this genotype were detected before the documented importation events.

Altogether the results suggest widescale rapid spread of BA.1.1 in Finland. COVID-19 patients hospitalized at HUH pulmonary or intensive care units showed similar, albeit delayed, lineage turnover from Delta variant to Omicron variant (Appendix Figure 4), consistent with population-level data.

Conclusions

We characterize the rapid increase in incidence of the SARS-CoV-2 Omicron variant in Finland. Specifically, our data suggest that BA.1.1 rapidly emerged as the dominant lineage over its parent, BA.1. The BA.1.1 lineage-defining R346K substitution in the spike protein has been suspected of increasing transmission rates more than the BA.1 lineage. This substitution, which occurred convergently in the Mu variant of concern, provides evidence of positive selection (*1*,*5*) and affects antibody binding (*6*). Although this mutation might provide an additional transmission advantage through enhanced immune-escape properties in a population, alternative options such as the founder effect cannot be ruled out for explaining the rapidly established dominance of this lineage in Finland.

Overall, Finland represents one of the countries with a rapid surge of Omicron variant BA.1.1 lineage introduced into a population largely vaccinated with 2 shots and within an epidemiologic landscape of increasing Delta circulation and absent or very low BA.2 circulation. These dynamics resulted in the dominance of BA.1.1 over both the Omicron BA.1 and Delta strains. Our study exemplifies the need for genomic surveillance and rapid detection of emerging SARS-CoV-2 lineages to support public health response and mitigation efforts.

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Appendix

SARS-CoV-2 testing

During the study period, 29 Nov 2021 to 6 Jan 2022, SARS-CoV-2 was tested by reverse transcriptase PCR (RT-PCR) on three different occasions: 1) from travelers entering the country (https://raja.fi/en/guidelines-for-border-traffic-during-pandemic), 2) by testing asymptomatic people needing travel documentation and 3) symptom-based testing according to recommendations of each hospital district in Finland. Until the explosive rise in SARS-CoV-2 Omicron infections, the testing capacity was able to handle the symptom-based testing and contact tracing was partially able to resolve chains of transmission. However, with case numbers rising exponentially towards the end of 2021, healthy individuals with mild COVID-19 symptoms were recommended to perform lateral flow antigen testing on their own and stay home. Therefore, the reported COVID-19 cases might be underreported.

SARS-CoV-2 testing by RT-PCR was conducted in diagnostic laboratories throughout Finland. For S-gene target failure (SGTF, a dropout of the S-gene PCR product due to deletion targeting residues 69-70 in the spike protein coding region), Thermo Fisher TaqPath COVID-19 assay was used to analyze samples received by HUS Clinical Microbiology division. The assay was able to S-gene target failure is typical for Omicron variant lineages BA.1/BA.1.1. Since other SARS-CoV-2 lineages with deletion in this genome region (such as Alpha variant) have not been detected in Finland since early autumn of 2021, a sample with SGTF was considered as an Omicron BA.1/BA.1.1 suspect.

SARS-Cov-2 sequencing

Samples subjected to sequencing were collected by HUS Clinical Microbiology division and Finnish Institute for Health and Welfare (THL), and were sent to University of Helsinki for sequencing. The samples originated throughout Finland. In HUS Clinical Microbiology division, a subset of Omicron-suspected SGTF samples were selected for sequencing, as well as a all positive border entry samples and random subset of community samples (the latter two irrespective of SGTF status, i.e. not biased towards Omicron positivity). The sequenced subset of positive cases collected by THL was based on random community samples with a few exceptions of known contacts of the first Omicron positive cases detected in Finland. The RT-PCR of these samples was carried out in local diagnostic laboratories and selection for sequencing was done irrespective of SGTF status.

The Helsinki University Hospital (HUH) data set (Appendix Table) was obtained from patients who were receiving care on 7 January 2022 for a PCR-diagnosed COVID-19 infection in either Pulmonary Diseases ward or ICU (Appendix Table), resulting in altogether 15 sequenced Omicron and 15 Delta genomes. Based on SGTF status of the initial RT-PCR testing, the final Omicron and Delta sample numbers were 19 and 18, respectively. All patients were alive on data collection day Jan 25 2022 and were of Finnish origin with no travel abroad, except one resident of Poland with no available travel data.

RNA was extracted from nasopharyngeal swab specimens using either the MagNA Pure 96 Instrument (RocheMolecular Systems Inc. Plesanton, CA, USA) or QIAamp Viral RNA Kit (Qiagen, Hilden, Germany). cDNA synthesis was conducted using Lunascript RT SuperMix Kit (New England Biolabs, Ipswich, MA) with random hexamers and oligo dT. SARS-CoV-2-specific amplicons were generated using xGen Artic V4 NCoV-2019 primers (Integrated DNA Technologies Inc., Coralville, Iowa) spiked with additional primers designed for Omicron amplification (https://community.artic.network/t/sars-cov-2-v4-1-update-for-omicron-variant/342) using Q5 Hot Start HighFidelity 2X Master Mix (New England Biolabs). The PCR amplicons were purified using Optima DTR 96-well clean-up system (Edge BioSystems, San Jose, CA, USA), end-prepped with NEBNext End Prep enzyme (New England Biolabs), ligated with unique dual indexes (Integrated DNA Technologies Inc.) using NEBNext Ultra II Ligation Module (New England Biolabs), pooled with 48 or 96 samples in one pool and purified using SpriSelect beads (Beckman Coulter Life Sciences, Indianapolis, IN, USA). The index-ligated

amplicons were amplified with KAPA HiFi HotStart ReadyMix (Roche Sequencing Solutions Inc, Pleasanton, CA, USA) and standard Illumina P5 and P7 primers (P5, AATGATACGGCGACCACCGAGATCT and P7, CAAGCAGAAGACGGCATACGAGAT) and purified with SpriSelect beads (Beckman Coulter Life Sciences). The pools were quantitated using Qubit fluorometer (Thermo Fisher Scientific, Waltham, MA, USA) and sequenced either with Illumina MiSeq system using the v3 sequencing kit (600 cycles) or Illumina NovaSeq 6000 system with NovaSeq 6000 SP Reagent Kit v1.5 (500 cycles).

Sequence analysis

The metadata on sequence-confirmed Omicron cases was retrieved from the Finnish National Infectious Disease Register on Jan 21 2022. The data consisted of 964 cases collected between Nov 29 2021 and Jan 6 2022. Of these, 133 samples were collected at points of border entry (airports, harbors and land borders). Numbers of patients in each hospital district, demographic distribution and travel records are shown in Table 1.

The raw sequence reads were trimmed, quality filtered and assembled using fastp (*1*) and BWA-MEM (*2*) programs implemented in HAVoC pipeline (*3*). The lineage assignment was conducted using the pangolin tool (v 3.1.20) (*4*).

The sequences with less than 1 700 ambiguous nucleotide positions were included in the phylogenetic analysis, resulting in 870 Omicron sequences from Finland. A global subsample of Omicron sequences was constructed by identifying sequences closely related to the Finnish Omicron sequences using UShER tool (*5*) and retrieving these from GenBank and Gisaid databases. The global sequence data was further downsampled by removing identical sequences and accepting one representative of each clade per country.

The omicron sequences were aligned with nextalign (v 1.11.0) package from Nextclade (*6*) and the phylogenetic trees were inferred with maximum likelihood method implemented in IQTREE2 (v. 2.0.6) software (*7*) using ModelFinder (*8*) and 1 000 bootstrap replicates were computed with Ultrafast bootstrap algorithm (*9*). Cluster assignment was conducted with TreeCluster (v 1.0.3) (*10*) using an arbitrary branch length of 0.001 and support value of 70.

The statistical analyses were carried out using the web-based software Epitools (https://epitools.ausvet.com.au).

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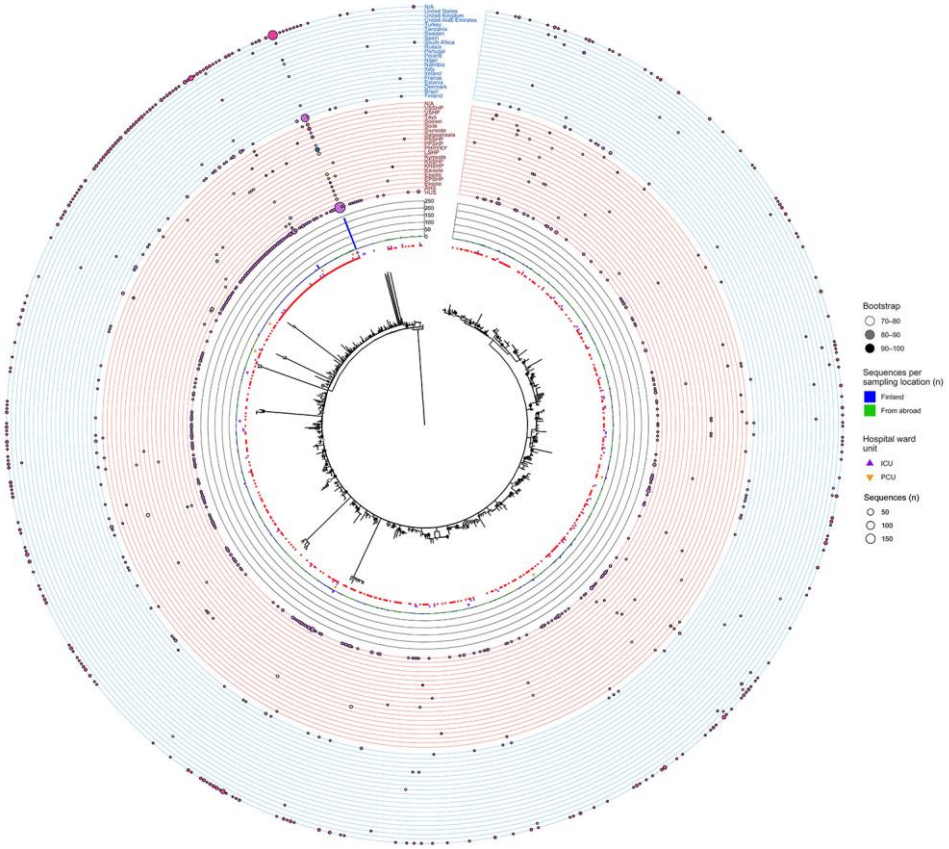
Appendix Table. Helsinki University Hospital SARS-CoV-2 positive patients receiving hospital care on January 7, 2022 on either pulmonary care unit or intensive care unit hospital ward*

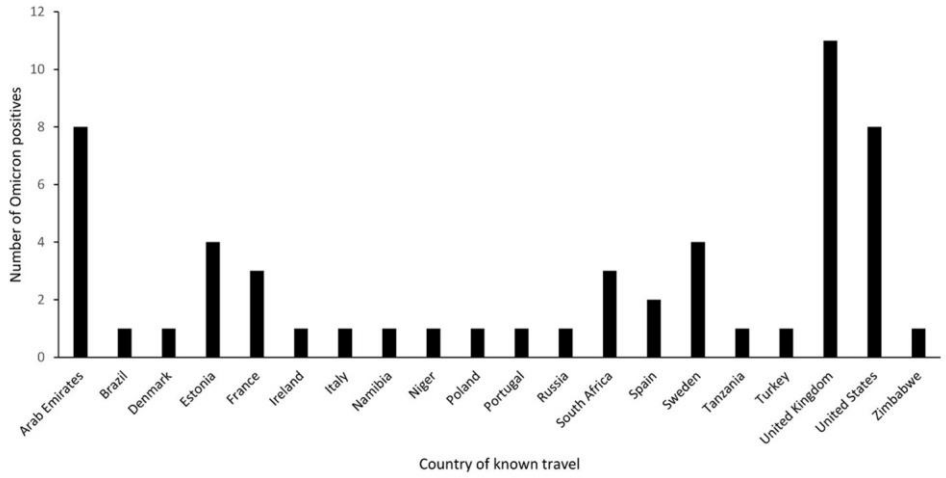
Patient	Sequence†	SGTF‡	Sampling date	Age	Sex	Ward§	Ward stay#, d
1	Delta	non-SGTF	2021 Dec 2	56	F	PCU	> 48/22
2	Delta	non-SGTF	2021 Dec 17	59	F	PCU	13/5
3	Delta	non-SGTF	2021 Dec 18	45	M	PCU	22/15
4	Omicron	SGTF	2021 Dec 21	73	M	PCU	21/0
5	NA	non-SGTF	2021 Dec 22	70	F	PCU	12/0
6	Delta	NA	2021 Dec 24	49	M	PCU	10/5
7	Delta	NA	2021 Dec 28	45	F	PCU	11/9
8	NA	SGTF	2021 Dec 30	29	F	PCU	5/0
9	NA	SGTF	2021 Dec 30	72	F	PCU	8/0
10	NA	SGTF	2021 Dec 31	56	M	PCU	8/0
11	NA	non-SGTF	2021 Dec 31	45	F	PCU	8/5
12	Omicron	NA	2022 Jan 3	77	F	PCU	18/0
13	Omicron	NA	2022 Jan 4	72	F	PCU	4/0
14	Delta	NA	2022 Jan 5	63	M	PCU	7/0
15	Omicron	NA	2022 Jan 6	66	M	PCU	>20/11
16	Delta	NA	2022 Jan 6	42	M	PCU	9/0
17	NA	SGTF	2022 Jan 1	68	F	PCU	3/0
18	Omicron	NA	2022 Jan 6	59	M	PCU	4/0
19	Omicron	NA	2022 Jan 6	83	F	PCU	7/0
20	Omicron	NA	2021 Dec 26	70	F	PCU	17/0
21	Omicron	NA	2021 Dec 30	70	M	PCU	9/0
22	Omicron	NA	2022 Jan 6	63	M	PCU	>20/4
23	Omicron	NA	2021 Dec 26	67	M	PCU	13/0
24	Omicron	NA	2022 Jan 4	61	F	PCU	7/0
25	Delta	NA	2022 Jan 6	42	F	PCU	7/0
26	Delta	NA	2022 Jan 2	35	M	PCU	10/0
27	Delta	non-SGTF	2021 Dec 3	56	F	ICU	>49/>48
28	Delta	non-SGTF	2021 Dec 14	66	M	ICU	28/13
29	Delta	non-SGTF	2021 Dec 21	59	M	ICU	19/11
30	Omicron	NA	2021 Dec 29	61	F	ICU	13/6
31	Delta	NA	2022 Jan 6	72	M	ICU	>21/>20
32	NA	non-SGTF	2022 Jan 1	47	M	ICU	11/7
33	Omicron	NA	2022 Jan 2	73	M	ICU	14/7
34	Omicron	NA	2022 Jan 6	60	M	ICU	>20/>20
35¶	Delta	NA	2021 Dec 20	35	M	ICU	>37/>35
36	Delta	NA	2021 Dec 31	70	F	ICU	>26/>25
37	Omicron	NA	2022 Jan 4	48	M	ICU	22/10

*SGTF, S-gene target failure; ICU, Intensive care unit, PCU, pulmonary care unit; NA, not available; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; d, days. †Sequence, SARS-CoV-2 sequence, Delta, Pangolin lineage B.1.617.2, Omicron, Pangolin lineage B.1.1.529. ‡SGTF in the initial SARS-Cov-2 RT-PCR. §Ward, Hospital ward unit on Jan 7 2022. ¶Patient with non-Finnish origin (Poland), travel status nor known. #Ward stay, length of stay at hospital ward/ICU ward.

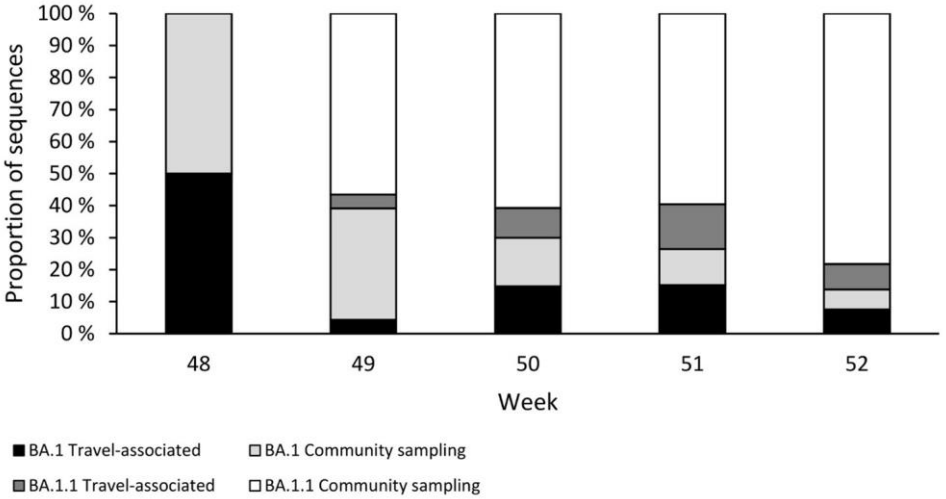


Appendix Figure 1. Clustering analysis of Finnish Omicron sequences. A collapsed maximum-likelihood phylogenetic tree of Omicron genomes sampled in Finland (n = 870) and reference sequences from abroad (n = 754), i.e. reference dataset. These are separated in the barplot in blue and green, respectively. The number of BA.1 and BA.1.1 sequences in each cluster are shown in the outermost barplot. Omicron sequences collected from the Finnish border are shown with purple squares. Clusters with border samples contain at most 1–9 sequences each. Clustering analysis reveals that by the beginning of January 2022, aside from one major BA.1.1 cluster (n = 236, which is 27.1% of all Finnish cases), the large majority of Omicron cases in Finland (n = 634, 72.8% of cases) were either singletons or minute clusters (≤30 sequences). The sampling location for each Omicron case in each cluster is shown with circles in two grids. The size of the circles indicate the number of sequences (n) from Finnish hospital districts (red grid) and from countries of infection (blue grid). Most of the sequences constituting the major clusters originated from local infections in Finland and were sampled in the Hospital District of Helsinki and Uusimaa (HUS). The tree was inferred with the IQTREE2 (v. 2.0.6) using ModelFinder and 1 000 bootstraps were computed with the integrated Ultrafast bootstrap algorithm, and the clusters (red squares) with TreeCluster (v. 1.0.3) using an arbitrary branch length of 0.001 and support value of 70. Sequences recorded from patients that were either in the intensive care unit (ICU) or pulmonary care unit (PCU) are indicated with triangles. The tree is rooted to a Omicron BA.2 sequence (Genbank: OV698431.1). Hospital district glossary: ÅHS = Åland Hospital District, Eksote = South Karelia Social and Health Care District, EPSHP = Hospital District of South Ostrobothnia, Essote = South Savo Social and Health Care Authority,

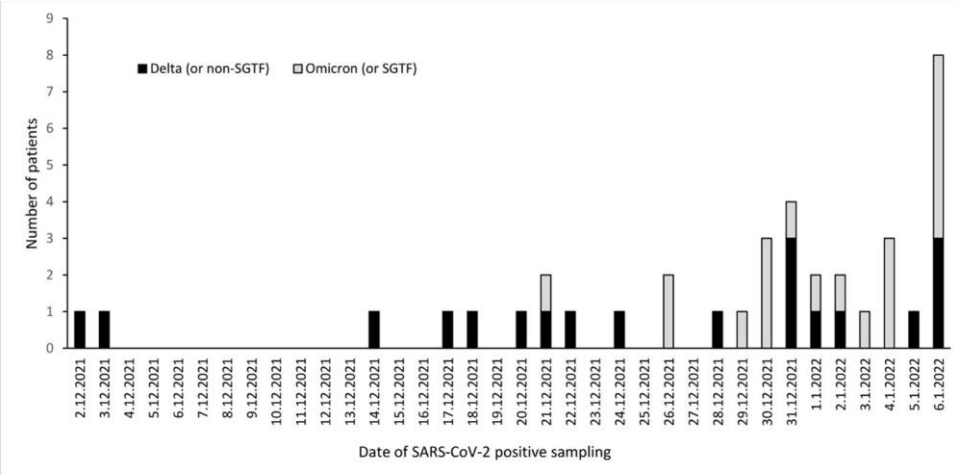
KHSHP = Tavastia Proper Hospital District, KSSHP = Central Finland Health Care District, Kymsote = Kymenlaakso social and health services, LSHP = Lapland Hospital District, PHHYKY = Päijät-Häme Hospital District, PPSHP = North Ostrobothnia Hospital District, PSSHP = North Savo Hospital District, Soite = Central Ostrobothnia Hospital District, Tays = Pirkanmaa Hospital District, VSHP = Vaasa Hospital District, Sosteri = East Savo Hospital District, Kaisote = Kainuu Social and Health Care Joint Authority, Siunsote = North Karelia Social and Health Care Authority, Satasairaala = Satakunta Hospital District, VSSHP = Southwest Finland Hospital District.



Appendix Figure 2. Finnish Omicron sequences with known traveling abroad. Travel data was obtained from 291/964 cases, of which 57 were reported abroad. 234 cases reported only domestic travel.



Appendix Figure 3. Weekly proportions of travel-associated and community sampling-derived Omicron variant lineages BA.1 and BA.1.1. Travel-associated was defined as sampled either at border or patient record indicating most likely country of infection abroad.



Appendix Figure 4. The onset of disease of the patients in the Pulmonary Care Unit or Intensive Care Unit with Omicron and Delta variants.